

# ADVANCES IN HEMATOLOGY

Current Developments in the Management of Hematologic Disorders

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## Chuvash Polycythemia: Diagnosis and Management

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### H&O What is Chuvash polycythemia?

**VG** Chuvash polycythemia is an inherited condition that affects hundreds of people in the Chuvash Republic of the Russian Federation. It was recognized in the 1970s by the Russian hematologist, Lydia Andreevna Polyakova, who identified that the condition was different from polycythemia vera, that it was a hereditary condition, and that the inheritance was autosomal recessive. Subsequent studies of Chuvash polycythemia in the past 10–12 years have shown that the condition is caused by a specific mutation in the *VHL* gene that results in an R200W amino acid substitution. The condition leads to increased levels of hypoxia inducible factor (HIF)-1 and HIF-2 and upregulation of the hypoxic response even when oxygen levels are normal. This results in increased concentrations of erythropoietin, the hormone that promotes production of red blood cells, which causes polycythemia (or erythrocytosis). There are many other genes that have altered regulation, which leads to a number of other manifestations as well. For example, there are changes in the inflammatory response and in glucose metabolism.

### H&O What are the associated symptoms and complications?

**VG** Patients with this condition may be identified by finding an increased hemoglobin and hematocrit on routine blood testing or by evaluation for a ruddy or red complexion due to the high hemoglobin concentration.

The diagnosis is confirmed by identifying the R200W mutation in *VHL* by molecular genetic testing.

Early in life there may be no symptoms, or the patient may complain of headache. As the patient enters adulthood, the condition is associated with markedly increased mortality. In a matched-cohort longitudinal study, only 29% of patients with Chuvash polycythemia were still alive by the age of 65 years compared to 64% of control individuals born in the same village. The mortality curves started to diverge by the age of 25 years.

There is a marked increase in stroke and other thrombotic events in these patients, although thrombosis does not account for all of the increased mortality. Paradoxically, there is an increase in bleeding events as well, and some of the strokes are hemorrhagic. Other complications include pulmonary hypertension and hemangiomas. All of the causes of the increased mortality in this condition have not been identified, but thrombotic complications and strokes are important components.

### H&O What is the role of von Hippel–Lindau (VHL) tumor suppressor gene mutations?

**VG** *VHL* is a gene involved in the hypoxia-sensing pathway. The VHL protein marks the alpha subunits of HIF-1 and HIF-2 for destruction by the proteasome when oxygen levels are normal. HIFs are transcription factors that are the master regulators of the body's response to hypoxia. The alpha subunits of HIFs are constantly produced and under normoxic conditions are degraded by a process that the VHL protein initiates. When cells are exposed

to hypoxia, these HIF subunits are no longer degraded by the process that VHL protein initiates; rather they survive, combine with a constitutive beta HIF subunit, and cause altered regulation of many different genes. In the case of Chuvash polycythemia, a mutation in the *VHL* gene causes impaired recognition of the alpha subunits of HIFs, so that there is impaired degradation of them under normoxic conditions. Increased levels of HIFs lead to an upregulation of the body's hypoxic response, even though there is no hypoxia present.

### H&O How is Chuvash polycythemia currently managed?

**VG** The optimal management of the condition is not known. Doctors in Chuvashia sometimes use phlebotomy, similar to the management of polycythemia vera. It is not known whether phlebotomy decreases complications or reduces mortality. At times the phlebotomy is performed in response to a symptom such as headache. Sometimes patients request phlebotomy to ameliorate the ruddy complexion. One concern is that frequent phlebotomy procedures can lead to iron deficiency because the hemoglobin in red cells is a major site of the body's iron. Iron deficiency can also promote the survival of the alpha subunits of HIF. Therefore, it seems possible that phlebotomy might exacerbate the underlying process of upregulated HIFs. In summary, it is not known if phlebotomy therapy is appropriate for Chuvash polycythemia. A useful area of research would be a controlled trial of phlebotomy in these patients if funding could be secured.

In the future, a potential therapeutic approach might be inhibitors of HIFs. If such agents are developed for clinical use—for the treatment of cancer, for example—it would be interesting to assess them in patients with Chuvash polycythemia.

### H&O What are some areas of research in Chuvash polycythemia?

**VG** There are pulmonary and metabolic complications to this condition that have not been completely elucidated. For example, Chuvash polycythemia patients have decreased glucose concentrations and decreased hemoglobin A1c levels, which reflect the average glucose levels over the preceding months. An interesting area of research would be to determine the mechanism of these decreased glucose levels, which could perhaps provide insight into new therapies for conditions such as diabetes mellitus. We do not fully understand what causes the thrombotic complications in this condition. Further research into this area might shed light into the associated coagulation pathways and present new targets to prevent thromboses in at-risk patients or to develop new anticoagulants based on the pathways that are observed. The hypoxic response affects so many different aspects of the body's metabolic, immune, and endocrine pathways that further research in Chuvash polycythemia could lead to many rich insights into various aspects of the body's metabolism.

### Suggested Readings

- Ang SO, Chen H, Hirota K, et al. Disruption of oxygen homeostasis underlies congenital Chuvash polycythemia. *Nat Genet.* 2002;32:614-621.
- Gordeuk VR, Prchal JT. Vascular complications in Chuvash polycythemia. *Semin Thromb Hemost.* 2006;32:289-294.
- Gordeuk VR, Sergueeva AI, Miasnikova GY, et al. Congenital disorder of oxygen-sensing; association of the homozygous Chuvash polycythemia VHL mutation with thrombosis and vascular abnormalities but not tumors. *Blood.* 2004;103:3924-3932.
- Miasnikova GY, Sergueeva AI, Nourai M, et al. The heterozygote advantage of the Chuvash polycythemia VHLLR200W mutation may be protection against anemia. *Haematologica.* 2011;96:1371-1374.
- Yoon D, Okhotin DV, Kim B, et al. Increased size of solid organs in patients with Chuvash polycythemia and in mice with altered expression of HIF-1alpha and HIF-2alpha. *J Mol Med (Berl).* 2010;88:523-530.